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[Print](#)

L2: Entry 8 of 16

File: USPT

Aug 20, 2002

DOCUMENT-IDENTIFIER: US 6436708 B1

TITLE: Delivery system for gene therapy to the brain

Abstract Text (1):

A gene delivery system which. is both safe and results in long-term expression throughout the brain has been developed. A lipid-entrapped, polycation-condensed DNA (LPD) system has been developed for brain gene delivery, using an adeno-associated viral ("AAV") vector in which the transcription unit is flanked by the 145 bp inverted terminal repeats (ITR) of the adeno-associated virus. This AAV plasmid is more effective than a non-ITR containing plasmid in vivo. The results show that the LPD-AAV plasmid complexes efficiently transduce neurons and that gene expression can persist for over 10 months in the brain. Furthermore, the intraventricular delivery method with systemic hyperosmolality results in global gene delivery. The examples show that expression of the human aspartoacyclase ("ASPA") gene in children with this metabolic disorder can be obtained over a period of many months to a year, with functional activity.

Brief Summary Text (9):

A gene delivery system which is both safe and results in long-term expression has been developed. The method yields widespread gene delivery throughout the brain. A lipid-entrapped, polycation-condensed DNA (LPD) system has been developed for brain gene delivery, using an adeno-associated viral ("AAV") vector in which the transcription unit is flanked by the 145 bp inverted terminal repeats (ITR) of the adeno-associated virus. This AAV plasmid is more effective than a non-ITR containing plasmid in vivo. In addition, an intraventricular delivery system has been developed to obtain widespread, global delivery.

Brief Summary Text (15):

A lipid-entrapped, polycation-condensed DNA (LPD) system for brain gene delivery has been developed. The LPD particles are small, about 60-80 nm, monodispersed and colloidally stable (Gao and Huang, 1996). These particles have been shown in vitro to be highly effective in transduction efficiency (approximating that of adenoviral vectors) and safe (Huang, 1997).

Detailed Description Text (15):Liposomes and PolycationsDetailed Description Text (16):

The liposome was made under sterile, good manufacturing processing ("GMP") conditions. The liposome is a mixture of the neutral lipid DOPE (dioleoyl phosphatidylethanolamine) with a cationic liposome, DC-Chol (3b-[N-(N',N'dimethylaminoethane) carbamoyl]cholesterol). The polycations used included poly-L-lysine (18,900 m.w., Sigma, St. Louis) and protamine sulfate (USP grade, Eli Lilly).

Detailed Description Text (21):

For immunocytochemical (ICC) analysis of brain sections, rats were deeply anesthetized with chloral hydrate and perfused with 1 M PBS (ph 7.3) followed by 4% paraformaldehyde (PF). Brains were removed and post-fixed (3-4 hours) in 4% PF followed by ascending sucrose solutions (10/15/30% in PBS). Sections (7-30 .mu.m)

were cut in a cyrostat (Reichert-Jung) and mounted on polylysine-coated slides. Sections were initially incubated in blocking buffer (5% goat serum (GS)/5 % normal horse serum (NHS) in 1 M phosphate buffered saline (PBS)), followed by 2-4 hours incubation at room temperature with mouse Ig antibody.

Detailed Description Text (92):

The following abbreviations were used herein: NGF--nerve growth factor; BDNF--brain derived neurotrophic factor; GDNF--glial cell line-derived neurotrophic factor; GABA--gamma-amino butyric acid; CNS--central nervous system; AAV--adeno-associated vector; ITR--inverted terminal repeats; LPD--lipid-entrapped, polycation-condensed DNA; bbb--blood-brain-barrier; CMV--cytomegalovirus; ASPA--aspartoacylase; GMP--guanosine monophosphate; DOPE--dioleoyl phosphatidylethanolamine; DC-Chol--3b-[N-(N',N'dimethylaminoethane)carbamoyl]cholesterol; EGTA--ethylene glycol-bis(.beta.-aminoethyl ether); ICC--immunocytochemical; PF--paraformaldehyde; GS--goat serum; NHS--normal horse serum; PBS--phosphate buffered saline; CSF--cerebral spinal fluid; NF--necrosis factor/nuclear factor/nerve factor/neurofibromatosis; GFAP--glial fibrillary acidic protein; NAA--N-acetylaspartate; H&E--hemotoxylin & eosin; MHC--major histocompatibility complex; HSV--herpes simplex virus; GPDS--Gesell-Provence Developmental Schedules; VEP--visual evoked potentials; CHOP--Childrens' Hospital of Philadelphia; NMRS--nuclear magnetic resonance scan; AEP--auditory evoked potentials.

Other Reference Publication (16):

Kim, et al., "Preparation of multivesicular liposomes," Biochim. Biophys. Acta 728:339-348 (1983).

Other Reference Publication (26):

Gao, et al., "Potentiation of cationic liposome-mediated gene delivery by polycations," Biochemistry 35:1027-1036 (1996).

CLAIMS:

1. A method for increasing gene expression in cells of the central nervous system comprising administering at or adjacent to cells of the central nervous system tissue, cation lipid associated polycation-condensed nucleic acid, wherein the cation lipid associated polycation-condensed nucleic acid comprises a cationic lipid, a polycation, and a nucleic acid encoding a protein associated with a genetic disorder, wherein the cation lipid associated polycation condensed nucleic acid enhances gene expression in the cells of the central nervous system, wherein the nucleic acid does not include an AAV coding sequence.
2. The method of claim 1 wherein the cation lipid associated polycation condensed nucleic acid comprises dioleoyl phosphatidylethanolamine.
4. The method of claim 1 wherein the polycations are selected from the group consisting of polylysine and protamine sulfate.
8. The method of claim 7 wherein the cation lipid associated polycation-condensed nucleic acid is administered intracerebrally.
9. The method of claim 4 wherein the lipid-entrapped polycation-condensed nucleic acid is administered intraparenchymally or intraventricularly.
10. A composition for increasing gene expression in cells of the central nervous system comprising cation lipid associated polycation-condensed nucleic acid, wherein the cation lipid associated polycation condensed nucleic acid comprises a cationic lipid, a polycation, and a nucleic acid encoding a protein associated with a neurogenetic disorder, wherein the cation lipid associated polycation condensed nucleic acid enhances gene expression in the cells of the central nervous system, wherein the nucleic acid does not include an AAV coding sequence.

11. The composition of claim 10 wherein the polycations are selected from the group consisting of polylysine and protamine sulfate.

12. The composition of claim 10 wherein the cation lipid associated polycation condensed nucleic acid comprise dioleoyl phosphatidylethanolamine.

18. The method of claim 1 wherein the administration of the cation lipid associated polycation-condensed nucleic acid at or adjacent to cells of the central nervous system tissue further comprises administering before or simultaneous with the delivery of nucleic acid to the central nervous system tissue a compound which causes hypersmolarity in the central nervous system tissue.

[Previous Doc](#)

[Next Doc](#)

[Go to Doc#](#)

## Hit List

Clear

Generate Collection

Print

Fwd Refs

Bkwd Refs

Generate OACS

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**Search Results - Record(s) 1 through 16 of 16 returned.**

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☐ 1. Document ID: US 6867195 B1

L2: Entry 1 of 16

File: USPT

Mar 15, 2005

US-PAT-NO: 6867195

DOCUMENT-IDENTIFIER: US 6867195 B1

TITLE: Lipid-mediated polynucleotide administration to reduce likelihood of subject's becoming infected

DATE-ISSUED: March 15, 2005

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Felgner; Philip L.	Rancho Santa Fe	CA		
Wolff; Jon Asher	Madison	WI		
Rhodes; Gary H.	Leucadia	CA		
Malone; Robert Wallace	Davis	CA		
Carson; Dennis A.	Del Mar	CA		

US-CL-CURRENT: 514/44

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Draw D
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☐ 2. Document ID: US 6812217 B2

L2: Entry 2 of 16

File: USPT

Nov 2, 2004

US-PAT-NO: 6812217

DOCUMENT-IDENTIFIER: US 6812217 B2

TITLE: Medical device and methods of use

DATE-ISSUED: November 2, 2004

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hendriks; Marc	Brunssum			NL

US-CL-CURRENT: 514/44; 424/450, 435/320.1

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Draw. D
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☐ 3. Document ID: US 6649357 B2

L2: Entry 3 of 16

File: USPT

Nov 18, 2003

US-PAT-NO: 6649357

DOCUMENT-IDENTIFIER: US 6649357 B2

TITLE: Apparatus and method for detecting and identifying infectious agents

DATE-ISSUED: November 18, 2003

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bryan; Bruce J.	Beverly Hills	CA		
Gaalema; Stephen	Colorado Springs	CO		
Murphy; Randall B.	Irvington	NY		

US-CL-CURRENT: 435/7.1, 356/215, 356/222, 356/317, 422/57, 422/58, 422/68.1,  
422/82.05, 422/82.08, 435/288.7, 435/6, 435/7.9, 435/808, 435/973, 435/975,  
436/164, 436/172, 436/518, 436/524, 436/527, 436/532, 436/805

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Draw. D
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☐ 4. Document ID: US 6649356 B2

L2: Entry 4 of 16

File: USPT

Nov 18, 2003

US-PAT-NO: 6649356

DOCUMENT-IDENTIFIER: US 6649356 B2

TITLE: Apparatus and method for detecting and identifying infectious agents

DATE-ISSUED: November 18, 2003

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bryan; Bruce J.	Beverly Hills	CA		
Gaalema; Stephen	Colorado Springs	CO		
Murphy; Randall B.	Irvington	NY		

US-CL-CURRENT: 435/7.1, 356/215, 356/222, 356/317, 422/57, 422/58, 422/68.1,  
422/82.05, 422/82.08, 435/288.7, 435/6, 435/7.9, 435/808, 435/973, 435/975,  
436/122, 436/164, 436/518, 436/524, 436/527, 436/532, 436/805

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Draw. D
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☐ 5. Document ID: US 6642024 B1

L2: Entry 5 of 16

File: USPT

Nov 4, 2003

US-PAT-NO: 6642024

DOCUMENT-IDENTIFIER: US 6642024 B1

TITLE: Guanylate-binding protein

DATE-ISSUED: November 4, 2003

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pennica; Diane	Burlingame	CA		

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 435/325, 530/350, 536/23.1

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Drawn De
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☐ 6. Document ID: US 6458547 B1

L2: Entry 6 of 16

File: USPT

Oct 1, 2002

US-PAT-NO: 6458547

DOCUMENT-IDENTIFIER: US 6458547 B1

TITLE: Apparatus and method for detecting and identifying infectious agents

DATE-ISSUED: October 1, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bryan; Bruce J.	Beverly Hills	CA		
Gaalema; Stephen	Colorado Springs	CO		
Murphy; Randall B.	Irvington	NY		

US-CL-CURRENT: 435/7.1; 356/215, 356/222, 356/317, 422/57, 422/58, 422/82.05,  
422/82.08, 435/288.7, 435/6, 435/808, 435/973, 435/975, 436/172, 436/527, 436/805

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Drawn De
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☐ 7. Document ID: US 6441158 B1

L2: Entry 7 of 16

File: USPT

Aug 27, 2002

US-PAT-NO: 6441158

DOCUMENT-IDENTIFIER: US 6441158 B1

**\*\* See image for Certificate of Correction \*\***

TITLE: Oligomers that bind to ku protein

DATE-ISSUED: August 27, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dynan; William S.	Augusta	GA		
Yoo; Sunghan	Augusta	GA		

US-CL-CURRENT: 536/24.5; 536/23.1

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Draw D
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☐ 8. Document ID: US 6436708 B1

L2: Entry 8 of 16

File: USPT

Aug 20, 2002

US-PAT-NO: 6436708

DOCUMENT-IDENTIFIER: US 6436708 B1

TITLE: Delivery system for gene therapy to the brain

DATE-ISSUED: August 20, 2002

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Leone; Paola	Philadelphia	PA	19107	
During; Matthew J.	Philadelphia	PA	19147	
Sorgi; Frank L.	Sonoma	CA	95476	

US-CL-CURRENT: 435/458; 424/450, 435/320.1, 435/455, 514/44

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Draw D
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☐ 9. Document ID: US 6083926 A

L2: Entry 9 of 16

File: USPT

Jul 4, 2000

US-PAT-NO: 6083926

DOCUMENT-IDENTIFIER: US 6083926 A

**\*\* See image for Certificate of Correction \*\***

TITLE: Water soluble vitamin B.sub.12 receptor modulating agents and methods related thereto

DATE-ISSUED: July 4, 2000

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Morgan, Jr.; A. Charles	Mill Creek	WA		
Wilbur; D. Scott	Edmonds	WA		
Pathare; Pradip M.	Seattle	WA		

US-CL-CURRENT: 514/52; 436/505, 514/12, 514/2, 514/21, 514/387, 514/8, 530/350,  
530/367, 530/370, 530/395, 530/409, 530/825, 536/26.4, 536/26.41, 548/303.7

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Draw D
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☐ 10. Document ID: US 6034135 A

L2: Entry 10 of 16

File: USPT

Mar 7, 2000

US-PAT-NO: 6034135

DOCUMENT-IDENTIFIER: US 6034135 A

**\*\* See image for Certificate of Correction \*\***

TITLE: Dimeric cationic lipids

DATE-ISSUED: March 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schwartz; David Aaron	Encinitas	CA		
Dwyer; Brian Patrick	San Diego	CA		
Daily; William J.	Atascadero	CA		
Srinivasan; Kumar	San Diego	CA		
Brown; Bob Dale	Encinitas	CA		

US-CL-CURRENT: 514/616; 514/44, 514/478, 514/479, 514/563, 560/158, 564/153,  
564/154

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Draw D
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☐ 11. Document ID: US 5891689 A

L2: Entry 11 of 16

File: USPT

Apr 6, 1999

US-PAT-NO: 5891689

DOCUMENT-IDENTIFIER: US 5891689 A

TITLE: Heme-bearing microparticles for targeted delivery of drugs

DATE-ISSUED: April 6, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Takle; Garry B.	New York	NY		
George; Shaji T.	New York	NY		

US-CL-CURRENT: 435/458; 424/450, 435/174, 435/456, 514/44

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Draw D
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☐ 12. Document ID: US 5877220 A

L2: Entry 12 of 16

File: USPT

Mar 2, 1999

US-PAT-NO: 5877220

DOCUMENT-IDENTIFIER: US 5877220 A

TITLE: Amide-based oligomeric cationic lipids

DATE-ISSUED: March 2, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schwartz; David Aaron	Encinitas	CA		
Dwyer; Brian Patrick	San Diego	CA		
Daily; William J.	Atascadero	CA		
Srinivasan; Kumar	San Diego	CA		
Brown; Bob Dale	Encinitas	CA		

US-CL-CURRENT: 514/626; 514/479, 514/613, 564/193, 564/197

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	RMK	Draw D
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☐ 13. Document ID: US 5869465 A

L2: Entry 13 of 16

File: USPT

Feb 9, 1999

US-PAT-NO: 5869465

DOCUMENT-IDENTIFIER: US 5869465 A

**\*\* See image for Certificate of Correction \*\***

TITLE: Methods of receptor modulation and uses therefor

DATE-ISSUED: February 9, 1999

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Morgan, Jr.; A. Charles	Edmonds	WA		
Wilbur; D. Scott	Edmonds	WA		

US-CL-CURRENT: 514/52; 536/26.4, 536/26.44

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	RMK	Draw D
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☐ 14. Document ID: US 5840880 A

L2: Entry 14 of 16

File: USPT

Nov 24, 1998

US-PAT-NO: 5840880

DOCUMENT-IDENTIFIER: US 5840880 A

**\*\* See image for Certificate of Correction \*\***

TITLE: Receptor modulating agents

DATE-ISSUED: November 24, 1998

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Morgan, Jr.; A. Charles	Edmonds	WA		
Wilbur; D. Scott	Edmonds	WA		

US-CL-CURRENT: 536/26.4; 536/26.44

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWAC	Draw. D.
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☐ 15. Document ID: US 5840712 A

L2: Entry 15 of 16

File: USPT

Nov 24, 1998

US-PAT-NO: 5840712

DOCUMENT-IDENTIFIER: US 5840712 A

**\*\* See image for Certificate of Correction \*\***

TITLE: Water soluble vitamin B.sub.12 receptor modulating agents and methods related thereto

DATE-ISSUED: November 24, 1998

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Morgan, Jr.; A. Charles	Mill Creek	WA		
Wilbur; D. Scott	Edmonds	WA		
Pathare; Pradip M.	Seattle	WA		

US-CL-CURRENT: 514/52; 536/26.4, 536/26.44

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWAC	Draw. D.
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☐ 16. Document ID: US 5739287 A

L2: Entry 16 of 16

File: USPT

Apr 14, 1998

US-PAT-NO: 5739287

DOCUMENT-IDENTIFIER: US 5739287 A

TITLE: Biotinylated cobalamins

DATE-ISSUED: April 14, 1998

## INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wilbur; D. Scott	Edmonds	WA		
Pathare; Pradip M.	Seattle	WA		
Morgan, Jr.; A. Charles	Camino Island	WA		

US-CL-CURRENT: 530/367; 530/409, 536/26.4, 536/26.41, 548/303.7

Full	Title	Citation	Front	Review	Classification	Date	Reference			Claims	KWIC	Draw D
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Clear	Generate Collection	Print	Fwd Refs	Bkwd Refs	Generate OACS
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Terms	Documents
(multivesicular) and (polylysine or polycation)	16

Display Format:  [Previous Page](#)   [Next Page](#)   [Go to Doc#](#)